“New Approaches for Targeted & Responsive Imaging Agents“

NIBIB Workshop on **Defining the State-of-the-Art in Biomedical Imaging Research Needs for the Future**

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How might one increase the "sensitivity" of MRI agents for reporting molecular events *in vivo*?

- Maximize the relaxivity of Gd^{3+}-based agents (new structures, polymeric materials, novel formulations)

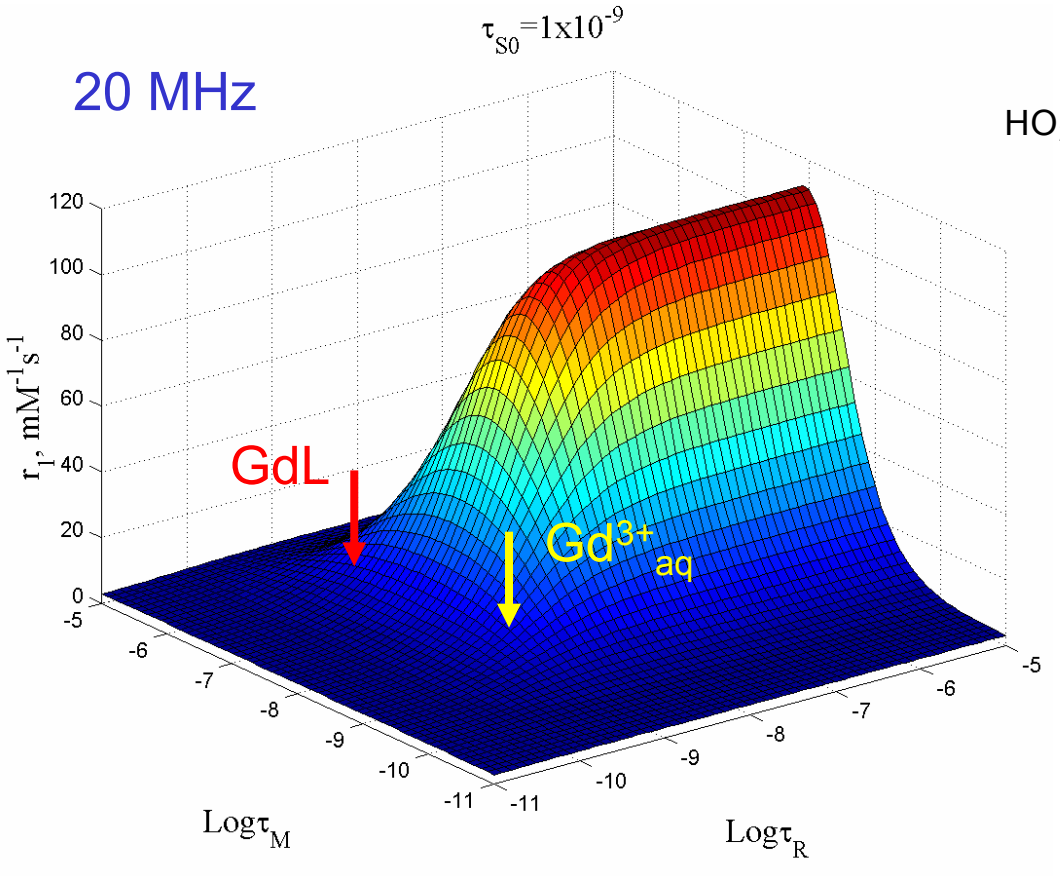
  1) What have we learned from basic physical chemistry studies?

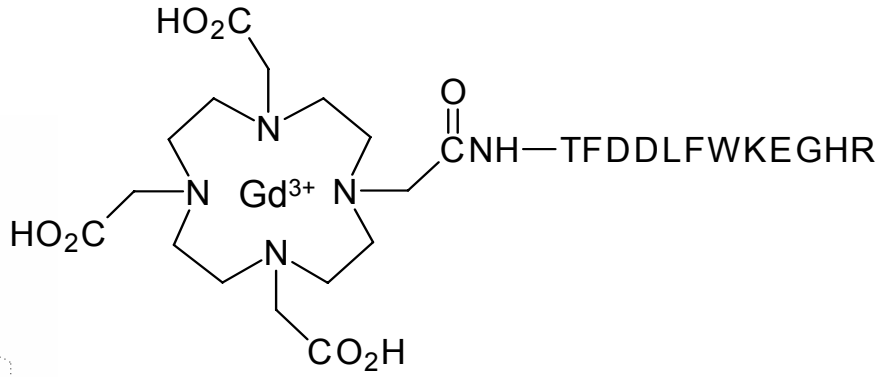
     Optimize τ_S, τ_R and τ_M (τ_M may be the most interesting)

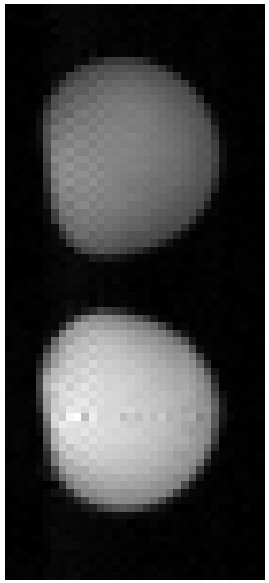
- New mechanisms for introducing image contrast (CEST agents, paramagnetic CEST agents)

  1) Are they potentially more sensitive than Gd^{3+}-based T_1 agents for molecular imaging?

Solomon-Bloembergen-Morgan theory for paramagnetics







25 μM Gd-peptide

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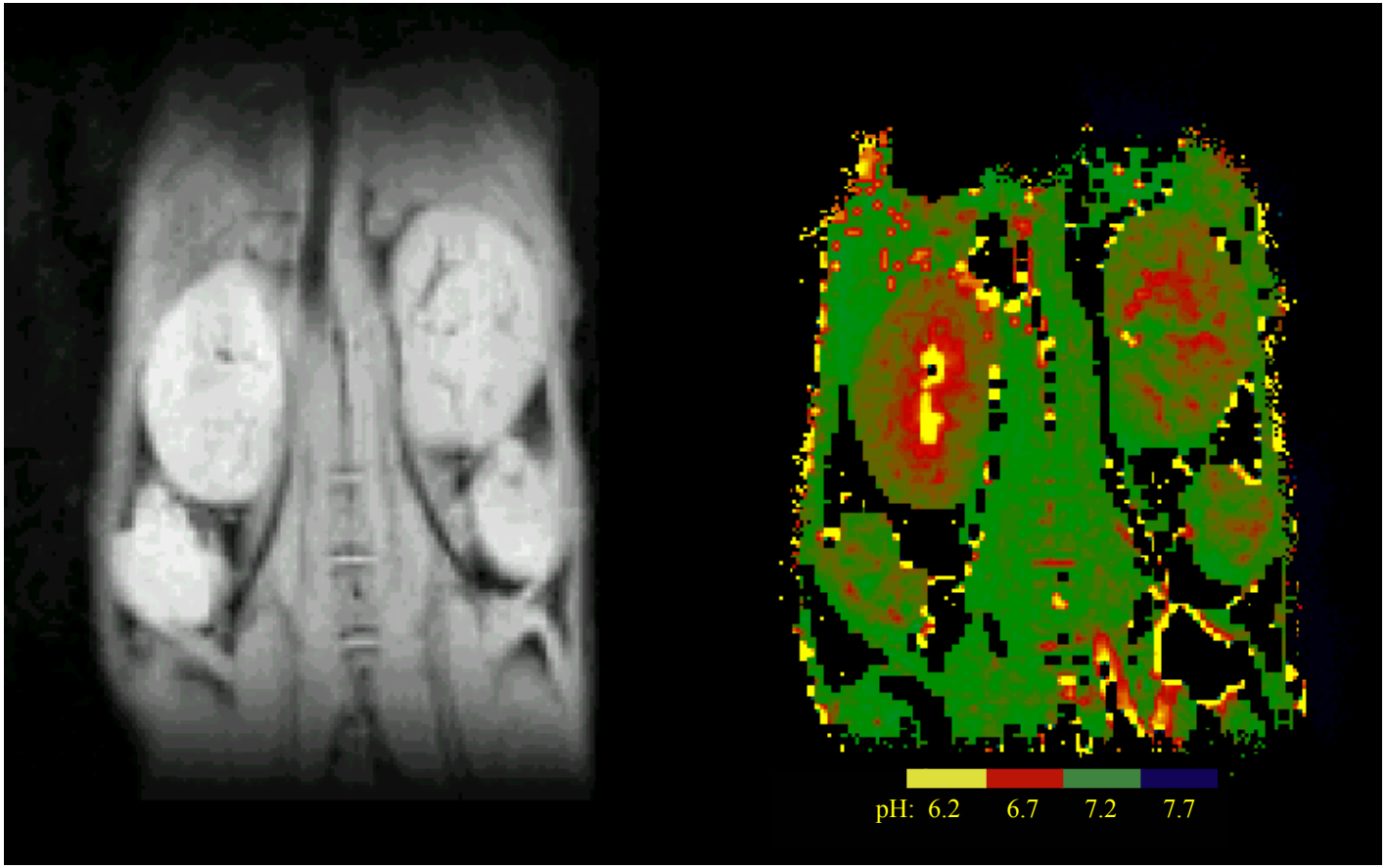
+ 25 μM GAL-80

De León, et al., JACS, **124**, 3514-3515 (2002)

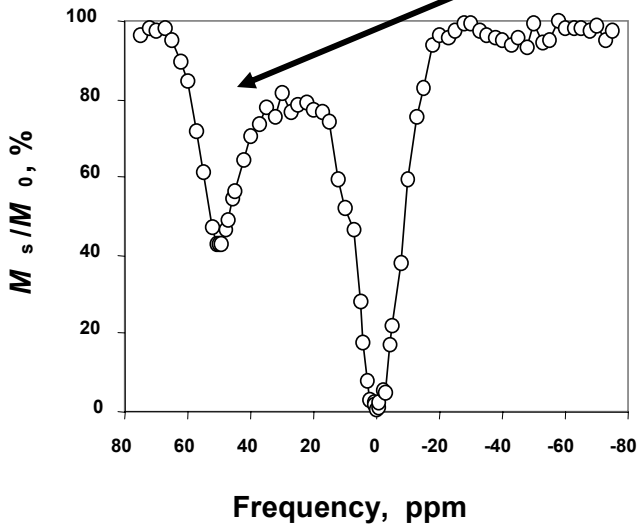
An image map of extracellular pH

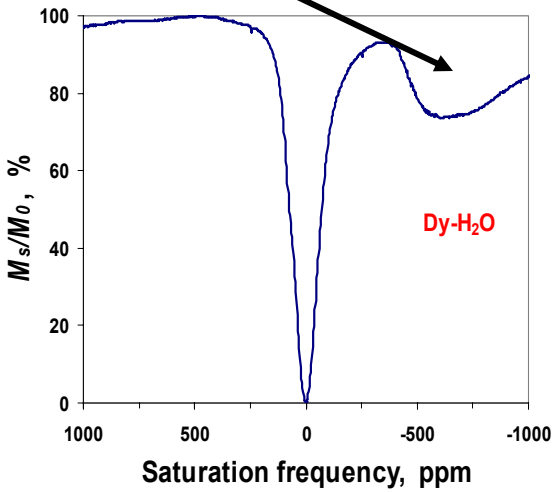


A fat-suppressed proton-density-weighted anatomic image of a female SCID mouse (left) showing the kidneys and ovaries. The right panel depicts the corresponding pH image using GdDOTA-4AmP & GdDTPA for subtraction (ref: Raghunand, C Howison, AD Sherry, S Zhang & RJ Gillies, Magn. Reson. Med., **49** , 249-257 (2003)).

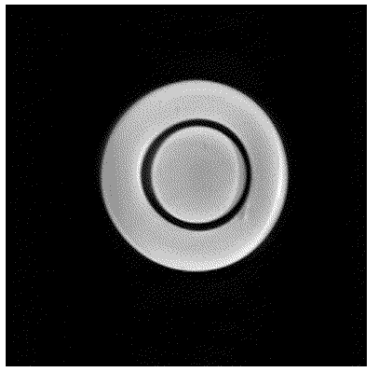
ParaCEST agents: complexes with slow water exchange

58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	**Pr**	**Nd**	**Pm**	**Sm**	**Eu**	**Gd**	**Tb**	**Dy**	**Ho**	**Er**	**Tm**	**Yb**	**Lu**

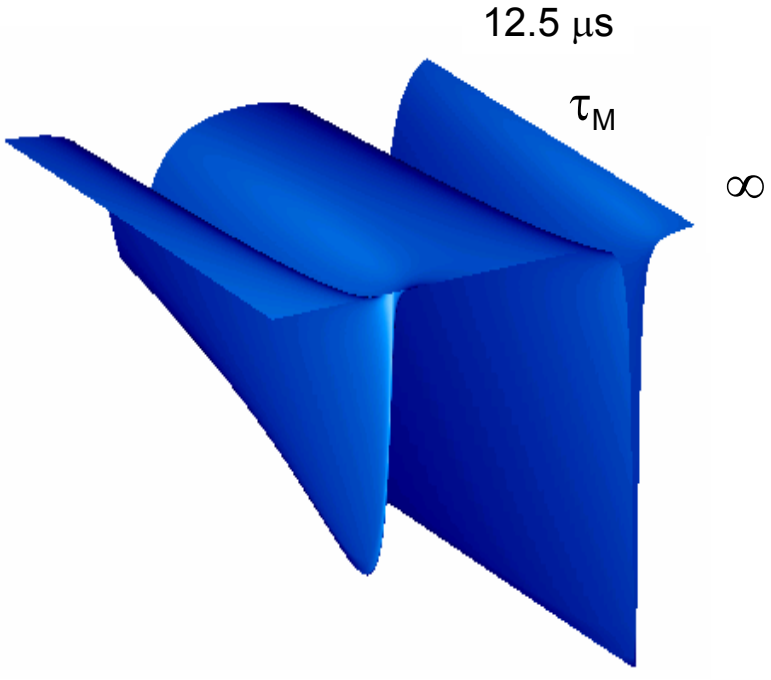




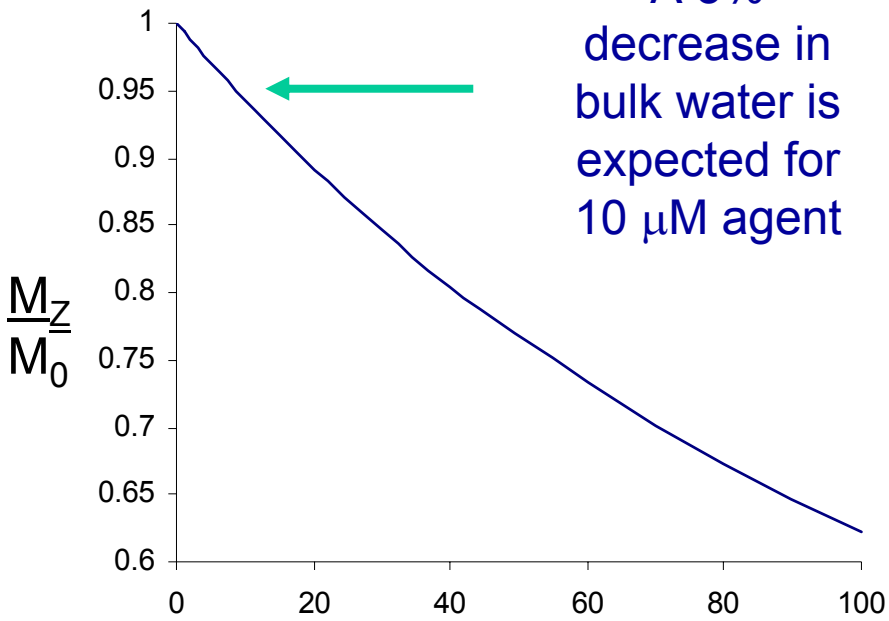
The contrast effect may be modulated



How sensitive is the paraCEST effect?



LnL complex with bound water at +500 ppm



Research Priorities

Priority #1: Chemistry

a) New ligands for MR, NucMed, PET and optical spectroscopy

Progress in imaging is limited by the availability of common paramagnetic complexes, novel ligands, and reactive intermediates for making new systems.

Priority #2: Responsive MR agents

a) sensitivity issues; increasing the magnitude of the MR response

b) Gd^{3+} *versus* other metal ions, paraCEST agents, modulation of the MR signal (OFF versus ON)